PATENT COOPERATION TREATY

PCT/EP2009/053385

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

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- 5. Okt. 2010
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PATENTANWÄLTE RECHTSANWÄLTE (GbR)

Date of mailing *(day/month/year)*	
30 September 2010 (30.09.2010)	
Applicant's or agent's file reference	IMPORTANT NOTICE
133680 aa/se	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2009/053385	23 March 2009 (23.03.2009)	21 March 2008 (21.03.2008)

Applicant: ABLYNX NV et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

Dies wurde durch die TA **nicht** *vorab an Mandanten verschickt!* Auf Wunsch von:
☐ Mandant ☒ zust. HE-Anwalt
Bitte ☑ ***nur*** zur Info
☐ mit Kommentar
an Mandanten weiterleiten. Danke!

(A014) ACHTUNG!
Mandant ggf. darauf hinweisen, dass mit einer Beanstandung nach Regel 161/162 (EP-Phase) zu rechnen ist.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 133680 aa/se	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2009/053385	International filing date *(day/month/year)* 23 March 2009 (23.03.2009)	Priority date *(day/month/year)* 21 March 2008 (21.03.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ABLYNX NV		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 21 September 2010 (21.09.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Agnes Wittmann-Regis e-mail: pt06.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2009/053385	23.03.2009	21.03.2008

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/727 A61K31/616 A61P7/02

Applicant
ABLYNX NV

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Weisser, Dagmar Telephone No. +49 89 2399-7266

Form PCT/ISA/237 (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☒ furnished subsequently to this Authority for the purposes of search.

4. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-2, 9-11, 14-19, 23

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-2, 9-11, 14-19 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 23

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item III.

The subject-matter of the claims 1,2,9-11,14-19, namely a "vWF binder", is defined by means of functional features. Because of the character of the functional features, i.e. being a binder, it cannot be guaranteed that the performed search is complete. It cannot be excluded that compounds fulfilling the requirements of the functional feature that have not been identified in the application have also not been covered by the search. Although the terms per se are clear, in a scientific sense, it is not clear which compounds of the prior art would also have said function, if they have not been identified as such in the present application.

Claim 23 refers to "all novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples". Such a formulation of the subject-matter claimed contravenes the requirements of Rule 6(2)(a) and Rule 6(3)(a) as the matter for which protection is sought is not defined in terms of the technical features. Hence, no search can be done on claim 23.

Re Item V.

Reasoned statement with regard to novelty, inventive step; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 2006/122825 A2 (ABLYNX NV [BE]; SILENCE KAREN [BE]) 23 November 2006 (2006-11-23)

D2: SILENCE KAREN ET AL: "ALX-0081 NANOBODY (TM), AN ENGINEERED BIVALENT ANTI-THROMBOTIC DRUG CANDIDATE WITH IMPROVED EFFICACY AND SAFETY AS COMPARED TO THE MARKETED DRUGS" BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 108, no. 11, PT. 1, 1 November 2006 (2006-11-01) , page 269A, XP009085105 ISSN: 0006-4971

Claims 1,3-22 relate to the subject-matter which is considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the methods of medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

The clarity problems of item III notwithstanding, the following preliminary opinion concerning novelty and inventive step is given for the parts of the claims 1-22 that have been searched and are clear and which refer to the compounds defined by general terms as well as by the specific amino acid sequences and to the uses of such compounds.

Novelty:

The subject-matter of claims 1-22 was not disclosed in any prior art and seems to be novel.

Inventive step:

Even if novelty of claims 1-22 can be acknowledged, inventive step thereof does not appear to be present; the reasons being as follow:

Claim 1:

D1 is regarded to be the closest prior art and it discloses (see passages cited in the SR) disclosing:

- the Nanobodies and polypeptides ("vWF binders") against vWF (see for example, SEQ ID NOs: 90 and 98 (ie ALX-0081) sharing 100% homology with the claimed amino acid sequences of SEQ ID NO: 19 and 1, respectively), applied appr. in dose of 10 to 400 µg/kg,

- wherein said "vWF binders" can be use alone or in combination with further anti-thrombotic agents like Heparin, Aspirin, or Plavix,

- wherein said "vWF binders"are used for the treatment of conditions of platelet-mediated aggregation (ie reduction of thrombus formation) including unstable and stable angina, embolus formation, deep vain thrombosis, thromboembolic complications, arterial thrombosis, embolism, thrombosis following angioplasty,

- wherein Kd of said "vWF binders" is less than 500 nM, preferably less than 200 nM, more preferably less than 10 nM, such as less than 500 pM,

The subject-matter of claim 1 differs from the closest prior art only in that the "vWF binder" the prevention of thrombus formation in stabile angina is provided by patients undergoing elective PCI.

Therefore, the problem to be solved by the present application may be regarded as how to provide the prevention of thrombus formation in patients with stabile angina undergoing additional treatment.

As discussed above, the idea of using "vWF binders" (alone or in combination with further anti-thrombotic agents) for prevention or reduction of thrombus was known to the public prior to the filing date of the present application (see D1 or D2). Moreover,

the antithrombotic use of "vWF binders" in case of thrombosis following angioplasty has also been disclosed (see D1). Even if the use of said compounds in the group of patients with stable angina undergoing a further medical intervention, namely elective PCI, was not disclosed in any available prior art it was not shown as having any unexpected effect over it. Hence, starting from D1 or D2 in combination with the fact that PCI is commonly used with anti-thrombotic therapy, the use of "vWF binders" for the claimed purpose would be regarded only as an obvious alternative which comes within the scope of customary practice followed by the skilled artisan. Thus, inventive step of claim 1 cannot be acknowledged.

For the same reasons, also claims 2-5,12,13 are regarded to lack inventive step.

Claims 16,20 and 21:

Since also additonal features of claims 16,20 and 21, namely obtaining blood samples from the patients and measurement the % platelet aggregation are known from D1 they can make the subject-matter of these claims inventive.

Claims 6-11:

Even if the additional features of claims 6-11, namely the application schedule of ALX-0081 and its dose, or the way of the measurement of % of the platelet aggregation after 6 hours after administration of ALX-0081, were not disclosed not mentioned in any available prior art they cannot be contribute to the acknowledgement of inventiveness of these claims as they were not shown as having any addtional technical effect.

Claims 14,15,17-19 and 22:

Ther subject-matter of claims 14,15,17-19 and 22 relates to different diagnostic methods (ie a method for evaluating the efficacy of a therapy using a "vWF binder", or for deciding on the course of a therapy, or for identifying a patient disposed to respond favorably to ALX-0081) in which two different assays, namely a RICO or RIPA assay, are used to measure the % platelet aggregation, wherein said measured % values are 20% and 10%, respectively.

As shown in D1 and D2, the ristocetin based assay has already been employed for the measurement of the % platelet aggregation after administration of ALX-0081. Even if such % values if measured by RIPA or RICO assays were not disclosed in any available prior art, their setting would fall under the routine labour practice conducted by the skilled artisan not possessing inventive skills. Hence, inventive step of claims 14,15,17-19 and 22 cannot be acknowledged.

Re Item VII.

There is a spelling mistake in claim 14 as instead of "using" the term "usinf" is disclosed.